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APPENDIX

The following individuals participated in the conduct of the trial:

Clinical Sites: Wake Forest University School of Medicine (Winston-Salem NC): J. Regan, M. Bettmann, B. Kouri, L. Patella, P. Tesch; Lake Washington Vascular and Overlake Hospital (Bellevue, Wash): K. Gibson, B. Ferris, D. Pepper, T. Fortney, A. Ebert, C. Leafdale, H. Covert; University of Southern California Medical Center (Los Angeles, Calif): V. Rowe, F. Weaver, D. Hood, C. Pappas, S. Parese; Duke University School of Medicine (Durham, NC): C. Shortell, T. Williams, S. Finley; University of Pittsburgh-Shadyside (Pittsburgh, Pa): S. Hirsch, E. Dillavou, J. Brimmeier, T. Richardson.

Data and Safety Monitoring Board: Carlos Kase, MD (chair) and Ravin Davidoff, MD (Boston Medical Center), Howard Rowley, MD (University of Wisconsin-Madison), Mark Espeland, PhD (Wake Forest University School of Medicine).

Study Proctors: Mark Isaacs, MD, John Mauriello, MD, David Wright, MB, FRCS.

Transcranial Doppler Core Laboratory (Sentient Neurocare Services, Inc.)**:** Alex Razumovsky, PhD (independent reviewer), David Pilchard.

MRI Independent Review: Lyle R. Gesner, MD.

Perceptive Informatics: James Paskevitz, MD, Matthew Hayden.

Parexel Clinical Services: E. Carter, E. Leip, S. Zandman, T. Zuttermeister.

BTG International: D. Wright, J. Rush, G. Suplick, J. Barclay, K. Arcuri, E. Evans, C. Tedesco, P. Mussenden.

INVITED COMMENTARY

Peter Gloviczki, MD, *Rochester, Minn*

During the past decade, foam sclerotherapy has been widely used around the world for treatment of varicose veins, for ablation of the incompetent saphenous veins, for perforating veins, or for treatment of venous malformations. Although liquid forms of the two most frequently used sclerosing agents, sotradecol and polidocanol, are now approved by the Federal Drug Administration (FDA), the use of foam has no FDA approval in the United States. Two European consensus meetings concluded that foam sclerotherapy was a safe, effective, and minimally invasive treatment of varicose veins with a low rate of complications.[1,2]

Reported complications of foam sclerotherapy have been indeed rare.[3] In a prospective multicenter study, Guex et al[4] reported on side-effects of 12,173 sclerotherapy sessions, 6739 performed with foam. Forty-nine incidents (0.4%) occurred, 37 after administration of foam. There were 20 cases of transient visual disturbances; in 19 cases, foam or air block was used. One patient developed femoral vein thrombosis. In a systematic review of data of more than 9000 patients who underwent foam sclerotherapy, the rate of serious adverse effects, including pulmonary embolism and deep vein thrombosis, was less than 1%. The median rate of visual disturbance was 1.4%, headache occurred in 4.2%, and thrombophlebitis in 4.7%.

Concerns about the use of foam have been raised when Bush[5] and other authors[6,7] reported on cases of stroke after foam sclerotherapy in patients who had a patent foramen ovale. Factors believed to increase the risk of stroke included the use of air instead

of CO_2 to prepare the foam, large amount (>20 mL) of foam used during one session, large bubble size, failure to elevate the limb after treatment, and prolonged immobility.[6,8,9] Standardization of the bubble size using commercially prepared microfoam[10] and the replacement of air with CO_2 in the solution have been suggested to decrease the risk of neurologic complications.[11]

In a prospective, uncontrolled study published in this issue of the *Journal of Vascular Surgery*, Regan at al performed ablation of the great saphenous vein in 82 patients with chronic venous insufficiency using ultra-low nitrogen polidocanol microfoam. Sixty patients with evidence of microemboli in the middle cerebral artery were evaluated for microinfarction in the brain using magnetic resonance imaging (MRI) and for myocardial infraction measuring cardiac troponin-I. Eighty-one patients were followed for 28 days; duplex scanning confirmed occlusion of the saphenous vein in 88%. Only one patient (1.2%) had a transient (20 seconds long) visual disturbance, and none developed cerebral microemboli, myocardial infarction, or clinically significant pulmonary embolism.

While this study demonstrated that microfoam treatment of the saphenous vein in 60 patients with right-to-left shunt did not cause cerebral infarction, the lack of a control group of patients with bedside preparation of the foam clearly weakens the value of the information. Even with a control group, the study would have a high chance for Type II error since many more patients are needed to show any difference in the risk of complications. The number of patients would depend on the rate of subclinical microemboli, detected by the authors' technique in patients treated with foam prepared from an air-sclerosing solution mixture: a study that alone is needed to give us valuable information on the risk of using room air in foam for sclerotherapy.

The 10% risk of failed treatment by 28 days and other side-effects reported in this study are disconcerting. Adverse events included pain or discomfort in the treated limb in 45%, deep vein thrombosis occurred in 7.4%, and secondary procedures to express thrombus from the treated saphenous vein were needed in 13.5%. These complications are higher than what was reported in any previous study with foam, and further refinement of the technique presented here is clearly warranted.

There is a great need for minimally invasive treatment of millions of people with chronic venous disease. Endovenous thermal ablation with radiofrequency or laser has been a major step in the right direction to replace the traditional high ligation and stripping in many patients. Foam is also here to stay for treatment of varicose veins;[12,13] therefore, the authors' efforts to produce a safe product and a minimally invasive technique for venous ablation should be applauded. This prospective trial by Regan and colleagues was an important step in the right direction. However, further controlled clinical trials with a much larger number of patients are needed to answer two important questions on foam sclerotherapy: is ultra-low nitrogen polidocanol microfoam superior to room-air microfoam, and will ultra-low-nitrogen polidocanol microfoam prevent neurologic complications?

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